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EXAMINER

HAYES, ROBERT CLINTON

ART UNIT PAPER NUMBER

1647

9

DATE MAILED: 02/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

08/897,390

Applicant(s)

La Vail et al

Examiner

Robert C. Hayes, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Apr 27, 2000
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-38 is/are pending in the application.
- 4a) Of the above, claim(s) 36-38 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-35 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claims 1-38 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) ☐ All b) ☐ Some* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- *See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) ☒ Notice of References Cited (PTO-892)
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
- 18) ☒ Interview Summary (PTO-413) Paper No(s). 8
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other:

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DETAILED ACTION

1. Due to Applicants correctly pointing out certain inconsistencies in the previous Office action, the previous Office Action of 10/27/99 (paper #7) is vacated, and replaced by the instant Office Action.
2. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1647.

Election/Restriction

3. Applicant's election with traverse of Group I (claims 1-35) in Paper No. 6 is acknowledged.

The traversal is on the ground(s) that "it would not be a serious burden on the Examiner to search Groups I and II together", and that "Applicants believe all of the claims of Group I and Group II are so closely related, they should remain in the same application to preserve unity of invention". However, although "to preserve unity of invention" may be appropriate for a PCT application, such is not a basis for examination of an U.S. application. Moreover, as previously made of record, albino mammalian eyes are required in the "assay" method of Group II, whereas treatment of neurodegeneration "in a mammal" is required in the "treatment" methods of Group I. In other words, the methods of treating degeneration of retinal neurons in subjects of

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Group I possess different goals and require different administration protocols, reagents, and mammals to treat, which are not required in the method of Group II, and vice versa. These inventions are, therefore, patentably distinct, as further illustrated by each of these groups acquiring a separate status in the art as shown by their different classification (i.e., Class/subclass: 514/12 vs. 435/7.21). Therefore, the non-coextensiveness of the search and examination for each group would constitute an undue burden on the examiner to search and consider each of the separable groups with their recognized divergent subject matter, and for the reasons made of record. The requirement is still deemed proper and is therefore made FINAL.

Claims 36-38 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to non-elected inventions, the requirement having been traversed in Paper No. 6.

This application contains claims 36-38 drawn to an invention nonelected with traverse in Paper No. 6. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

4. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-35 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible asserted utility or a well established utility.

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While the specification asserts a specific and substantial utility for the instant invention, “*preventing* degeneration of retinal neurons ... caused by exposure to light or other environmental trauma... comprising administering to the mammal, prior to, during or following such exposure...” is not credible, because even normal aging results in death of neurons, which can not be “prevented” from naturally degenerating. Moreover, “inherited retinal degenerations”, “ischemic neuropathies”, “maculopathies”, etc. are all characterized by neuronal cell death, which have no known treatment, and therefore, cannot be prevented “prior to, during or following such exposure” (e.g., as it especially relates to claims 1, 13 & 21). Therefore, given the broadest reasonable interpretation consistent with that disclosed within the specification for the recitation, “*preventing* degeneration of retinal neurons” which requires not even the naturally occurring loss of a single neuron, is not credible, by definition.

Applicant is directed toward the Revised Interim Utility Guidelines, Federal Register, Vol.64, No.244, pages 71427-71440, Tuesday December 21, 1999.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-35 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible asserted utility or a well established utility

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for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

6. Claims 1-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing degeneration of the outer segment of photoreceptor cells following intraocular or systemic administration of the well known neurotrophic factors BDNF, CNTF, NT-3, aFGF, bFGF, IL-1 β , TNF- α and IGF-2, does not reasonably provide enablement for any method for "reducing" or "preventing" neurodegeneration of retinal neurons generically with structurally uncharacterized modified neurotrophic factors orally, subcutaneously, intravenously or intramuscularly. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification proposes a method of "reducing" or "preventing" degeneration of retinal neurons in a patient with a "therapeutically effective dose" of BDNF, CNTF, NT-3, aFGF, bFGF, IL-1 β , TNF- α and IGF-2. However, the sole disclosure provided in the specification is the variable effects of various neurotrophic factors on outer nuclear thickness (ONL) and photoreceptor rescue, in which no significant results were obtained for NGF, NT-3, EGF, PDNF, insulin, IGF-I and IL-6 (see Figure 2).

First, the state of the art is such that problems encountered before assessing whether treatment with a "therapeutically effective dose" of BDNF, CNTF, NT-3, aFGF, bFGF, IL-1 β ,

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TNF- α and IGF-, etc. reasonably occurs within the CNS are that neuronal cell damage often results in cell death, and that "administration" of neurotrophic factors to treat neurons requires solutions to not only bypassing the blood-brain barrier when treating CNS disorders but to selectively target responsive cells, if known, with enough neurotrophic factor to elicit any response (i.e., through specific receptor binding). For example, Sendtner (see Barinaga, pg. 773 (1994)) found that the neurotrophic factor CNTF is quickly taken up and degraded by the liver with a half life of 3 minutes (i.e., as it relates to claims 2, 7, 11-12, 18-19, 22, 27-28 & 34-35). Moreover, in this same publication it was reported (same column on pg. 773) that Regeneron's Phase III study on CNTF to treat ALS resulted in a substantial number of those receiving CNTF having not only serious side effects, but having actually fared worse on measures of muscle strength than did patients receiving placebos. Thus, because it is unclear how one could administer a "therapeutically effective dose" of any CNTF-derived neurotrophin (i.e., as it relates to claims 1, 2, 20 & 22), and by analogy any BDNF, NT-3, aFGF, bFGF, IL-1 β , TNF- α and IGF-2 polypeptide, for a sufficient time period to elicit any measurable response (i.e., as it especially relates to claims 7, 11-12, 18-19, 27-28 & 34-35), because it is unknown what parameters are required to be assayed in order to determine when, or if, the instant invention is "therapeutically effective" in treating any "pathological condition", and because it cannot be successfully extrapolated from the limited disclosed method measuring ONL thickness or photoreceptor cell rescue, whether the skilled artisan has successfully practiced Applicant's invention, it would

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require undue experimentation for the skilled artisan to discover how to make and use Applicants' invention, as currently claimed.

Second, in order to practice the full scope of the invention, regeneration of the damaged axons in these neurodegenerative disease states are required, in order to treat a mammal with a "therapeutically effective dose" to "reduc[e] or prevent [neuronal] degeneration", as claimed. However, without functional synaptogenesis, there is no functional regeneration, and therefore, no expectation that degeneration can be reduced or prevented, or that a regeneration/effective treatment of any neurological disorder or disease is possible; especially as it relates to the recited disease states claimed, in which neurons otherwise die. Regeneration does not occur either because processes fail to grow the necessary distance, they are in competition with other nearby neuronal processes not derived from the affected nerve, astrocytic scarring blocks axonal elongation, or because of misdirected axonal growth (e.g., see Jackowski, pgs. 309-310). In other words, neurons do not regenerate in the CNS (e.g., see Jackowski, pg. 305, last *pp*; as it especially relates to "preventing degeneration" in claims 1, 13, 20 & 29). In contrast, the instant description fails to provide any guidance on how to prevent damaged neurons from degenerating, or how to "prevent" any neuron from dying that is damaged (i.e., as it relates to the "pathological conditions" in claim 21, etc.), or how any of the unique disorders recited in the claims (e.g., as it relates to claim 21), each with their unique etiology, can be effectively treated in the CNS; nor how to assay such *in vivo*. For example, only the outer segment of photoreceptor cells can effectively be treated when damaged, versus any more severe type of retinal neuronal damage

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that results in cell death (see Rapp, pg. 971, Fig. 2; e.g., as it relates to claims 1, 13, 20, 21 & 29); thereby, being consistent with the unpredictable state of the art as discussed above, in which no treatment is further known in the art for these "pathological conditions", which include "inherited retinal degenerations", "ischemic neuropathies", "maculopathies", etc., which alternatively are all characterized by neuronal cell death (e.g., Merck Manual, pgs. 2231-2234). Thus, because the instant specification discloses no *in vivo* assays for determining when, or if, the Applicant's invention works *in vivo*, or when any "degeneration of retinal neurons" are "reduced" or "prevented", the current claims merely constitute an invitation to experiment how to use the invention, in light of the unpredictable state of the art in preventing death of dying neurons.

Third, although the specification does list various "pathological conditions" found within the nervous system, the specification fails to describe how the instant invention can be used to treat these conditions with a "therapeutically effective dose" of any BDNF, CNTF, NT-3, aFGF, bFGF, IL-1 β , TNF- α and IGF-2 polypeptide, as currently claimed, in that no "pathological condition" of retinal neurons is known, or disclosed, that is dysfunctional due to altered expression of BDNF, CNTF, NT-3, aFGF, bFGF, IL-1 β , TNF- α and IGF-2, or a "combination thereof". Further, it is not known nor disclosed how the severity of symptoms (which are also not recited) are related to the efficacy of BDNF, CNTF, NT-3, aFGF, bFGF, IL-1 β , TNF- α and IGF-2 or any neurotrophic factor; thereby, requiring undue experimentation to discover how to make and use Applicant's invention, as currently claimed.

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Lastly, the name "neurotrophic factor" alone (e.g., as it is defined on page 8 of the specification; as it relates to claims 1 & 20) encompasses any fragment, "derivatives or analogs thereof", or any biologically functional equivalent of BDNF, CNTF, NT-3, aFGF, bFGF, IL-1 β , TNF- α or IGF-2 related polypeptide; thereby, providing no structural characterization and little functional characteristics for how to make the "neurotrophic factors" required to practice the claimed method. The specification further fails to define what specific amino acids are critical for any neurotrophic-related function. In contrast, the skilled artisan would reasonably expect that random mutations to any neurotrophic protein (i.e., as encompassed by the current claim language) to make fragments, "derivatives or analogs thereof" would result in inactive neurotrophic factors, and therefore a method that does not work. For example, Rudinger states on page 3 that "it is impossible to attach a unique significance to any residue in a sequence. A given amino acid will not by any means have the same significance in different peptide sequences, or even in different positions of the same sequence". Rudinger then states on page 6 that "the significance of particular amino acid sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study". Therefore, the lack of guidance provided in the specification as to what minimal structural requirements are necessary for knowing how to make or use neurotrophic factors, in general, does not in itself provide sufficient guidance on what polypeptides could be made which retains the desired function of the instant invention, because any such random mutations manifested in a BDNF, CNTF, NT-3, aFGF, bFGF, IL-1 β , TNF- α or IGF-2 related

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polypeptide would be predicted to adversely affect the three-dimensional conformation of the polypeptide, without requiring undue experimentation to determine otherwise.

7. Claims 1-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite and incomplete for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In particular, no recitation is included that defines when "reducing or preventing degeneration of retinal neurons" is accomplished, as recited in the preamble, or what constitutes a "therapeutically effective dose" when different disease states with different symptoms, as well as different neurotrophic factors that possess different efficacies, are encompassed by the claims.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

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Claims 1-5 & 20-25 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 5,667,968. Although the conflicting claims are not identical, they are not patentably distinct from each other because each claim the overlapping embodiments of treating retinal neurons/photoreceptors with CNTF.

Conclusion

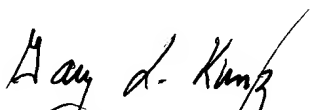
Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (703) 305-3132. The examiner can normally be reached on Monday through Thursday, and alternate Fridays from 8:30 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Robert C. Hayes, Ph.D.
February 4, 2002


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